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(54) Process for simvastatin.

(57) A process is disclosed, for the formation of simvastatin, which comprises the sequential acylation of a diol lactone to form a bis acylated intermediate followed by selective deacylation and lactone ring closure to form simvastatin.

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BACKGROUND OF THE INVENTION

Hypercholesterolemia is known to be one of the prime risk factors for atherosclerosis and coronary heart disease, the leading cause of death and disability in western countries. The bile acid sequestrants seem to be moderately effective as antihypercholesterolemic agents but they must be consumed in large quantities, i.e., several grams at a time, and they are not very palatable.

MEVACOR® (lovastatin), now commercially available, is one of a group of very active antihypercholesterolemic agents that function by limiting cholesterol biosynthesis by inhibiting the enzyme, HMG-CoA reductase. In addition to the natural fermentation products, mevastatin and lovastatin, there are a variety of semi-synthetic and totally synthetic analogs thereof. For example, simvastatin, wherein the 8-acyl moiety is 2,2-dimethylbutyryl, is an even more potent HMG-CoA reductase inhibitor than lovastatin.

Simvastatin is now commercially available as ZOCOR® in some markets.

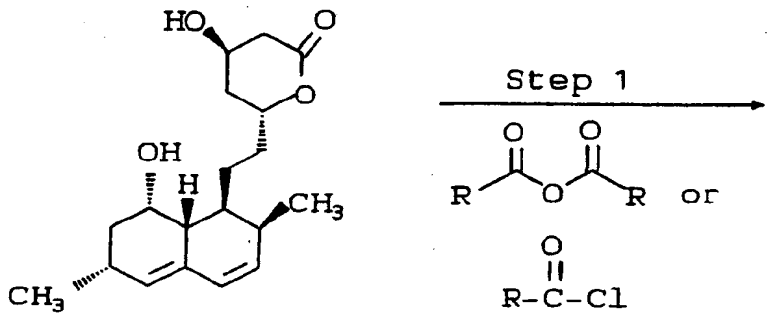
The preparation of simvastatin was originally described in U.S. Patent 4,444,784. The process involves deacylation of lovastatin followed by a subsequent acylation with the 2,2-dimethylbutyryl moiety. Simvastatin has also been prepared by the alpha alkylation of the lovastatin ester moiety as described in U.S. Patents 4,582,915 and 4,820,850.

The recent commercial introduction of simvastatin has provided a need for a high yielding process for the production of simvastatin, which is economically efficient and environmentally sound.

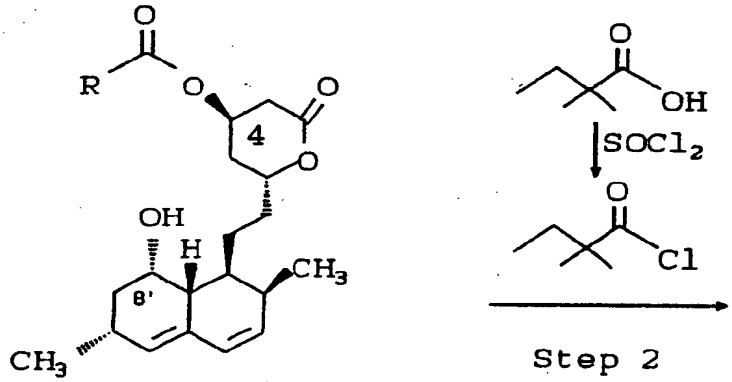
DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a process for the formation of simvastatin, which comprises the sequential acylation of a diol lactone (I) to form a bis acylated intermediate (III) followed by selective deacylation and lactone ring closure to form simvastatin (VI). The overall process is outlined in Scheme 1.

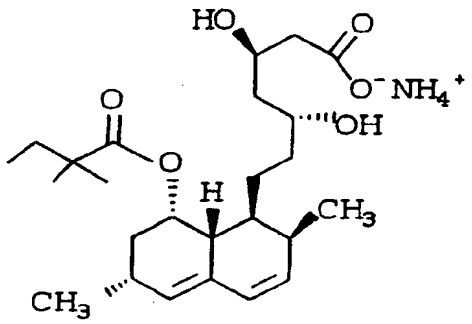
SCHEME 1



Diol lactone (I) R is C_{1-5} alkyl

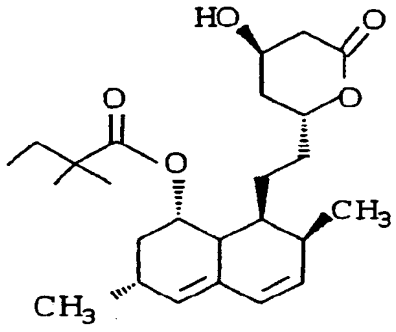


4-acyl diol lactone
(II)



Simvastatin ammonium salt
(V)

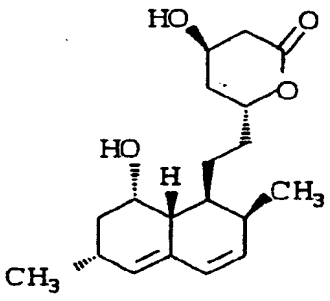
5. A process of Claim 4 further comprising the treatment of compound (V) with a dilute acid to form simvastatin (VI):



Simvastatin
(VI)

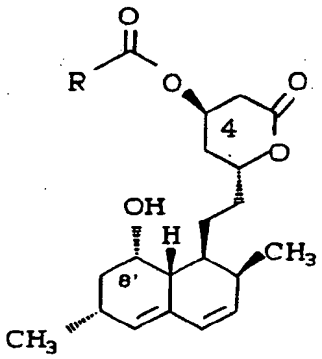
6. A process of Claim 5 wherein the dilute acid is selected from the group consisting of acetic, sulfuric and hydrochloric.

7. A process comprising the treatment of a diol lactone (I)



Diol lactone
(I)

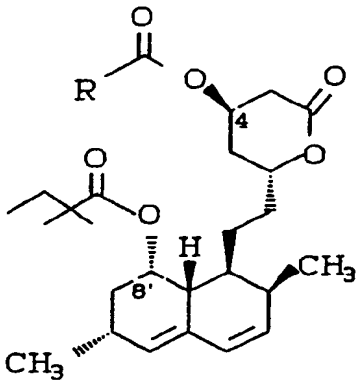
with an acylating agent selected from $(RCO)_2O$ or RCOCl, wherein R is C_{1-5} alkyl, to yield a compound (II):



4-acyl diol lactone

(II)

followed by treatment of compound (II) with 2,2-dimethylbutyryl chloride to yield a compound (III).



4-acyl simvastatin

(III)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 30 3920

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP-A-0 306 264 (MERCK AND CO. INC.) * page 10; example 13 *	1	C07C69/732 C07D309/30 C07C67/03 C07C67/28 C07D309/32

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07C
C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04 AUGUST 1992	KINZINGER J.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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